

Application No. 08/716,169  
Appeal No. 2004-1723  
Paper dated: October 19, 2004  
Attorney Docket No. 0470-961125

### **REMARKS**

Applicants at long last present herein new evidence and arguments that irrefutably show that the claimed invention is more than adequately enabled, and thus one skilled in the art at the time of filing of the application would have no difficulty practicing the invention without undue experimentation. Applicants respectfully submit that the new evidence and arguments categorically overcome the Examiner's enablement rejection by showing that the specification enables one skilled in the art to use the claimed heat shock proteins of the present invention predictably as anti-inflammatory compounds *in vivo*, that such use induce regulatory T cells *in vivo*, and that such compounds may be administered nasally, i.e. via the mucosal lining of the patient. The evidence and arguments are presented below in the following three sections.

The Notice of Appeal, filed March 25, 2003, in the above-identified patent application is dismissed, and jurisdiction of the above-identified patent application now is remanded back to the Examiner from the Board of Patent Appeals and Interferences for continued prosecution of the case pursuant to the filing of a Request for Continued Examination herewith. Claims 24-30 are currently pending in this application. Claims 31-32 have been added. Support for the recitations "parenterally, orally and nasally" contained in claims 31-32 is found on page 10, line 5. No new matter has been added. In view of this amendment and of the following remarks, Applicants believe that all the asserted rejections are in condition for withdrawal and all the claims are in condition for allowance.

Claims 24-30 stand rejected under 35 U.S.C. 112, first paragraph, for purported lack of scope of enablement. The Examiner asserts that Anderton et al. specifically teach administering mycobacterial heat shock proteins to treat diseases in animal models and that *in vivo* animal studies are not applicable for human treatment or protection in human disease due to the fact that humans are an outbred population and thus the use of the claimed peptides would be unpredictable. The Examiner further asserts that Applicants' argument that the present invention is directed to inducing regulatory T cells specific for heat shock protein is merely an assertion because there is no evidence of induction of regulatory T cells in Applicants' disclosure. Finally, the Examiner asserts that Wendling et al. teach that the nasal route of administration appears to be critical in treating autoimmune diseases with conserved heat shock proteins, that stimulation

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of IL-10 production for bystander suppression appears to be critical for tolerance induction, and that such a fine tuning of administration was not disclosed in the specification.

First, in response to the Examiner's assertion that there is no evidence of induction of regulatory T cells in Applicants' disclosure, the Examiner is directed to the Wendling et al. disclosure, which states in the last sentence of the introduction that, "the data presented here suggest that the induction of IL-10 producing cells with a regulatory phenotype is a characteristic feature of immunization with hsp." Furthermore, Wendling et al. state in the last paragraph:

[T]he present data have substantiated previous evidence that the arthritis suppressing quality of bacterial hsp immunization resides in conserved sequences of these molecules that have the potential of triggering self-hsp-reactive T cells. The regulatory phenotype (*inherent* or developing) of such T cells, characterized by IL-10 production, may be responsible for the mechanism through which such cells mediate bystander suppression targeted to sites of inflammation with up-regulated self-hsp. (emphasis added).

Applicants submit, therefore, that induction of regulatory T cells is inherent to the administration of the claimed heat shock peptides, thus explicit recitation in the specification that the claimed heat shock proteins induce regulatory T cells is unnecessary. Therefore, if the Examiner is entitled to rely on Wendling et al., then Wendling et al. should also be credited for disclosing the inherent induction of regulatory T cells after administration of the claimed heat shock proteins and for corroborating the very anti-inflammatory enablement which underlies the claimed invention.

Second, with respect to the Examiner's assertion that nasal administration, as disclosed by Wendling et al., is not disclosed in the present application, Applicants respectfully disagree and point the Examiner to page 10, line 5 of the specification, where nasal administration, as well as oral and parenteral administration, is disclosed, and which now is claimed in new claims 31 and 32. Additionally, the Examiner has characterized the route of administration question as "fine tuning." Enablement is not precluded by the necessity for some experimentation as long as that experimentation is not undue or unduly extensive, *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778, 785

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(Fed. Cir. 1988) *cert. denied*, 490 U.S. 1046 (1989), and “fine tuning” itself implies no undue experimentation.

Moreover, Applicants direct the Examiner to Chen et al. (“Regulatory T Cell Clones Induced by Oral Tolerance: Suppression of Autoimmune Encephalomyelitis,” *Science*, 265:1237-1240, 1994), full paragraph 2 to first sentence of paragraph 3 on page 1237, and first sentence of the last full paragraph on page 1240, which states:

Oral administration of antigens (oral tolerance) is a classic method of inducing antigen-specific peripheral immune tolerance. Orally administered antigens can induce active suppression (low antigen dose) or clonal anergy (high antigen dose). Oral tolerance is a biologically relevant method of inducing peripheral tolerance: it involves the physiologic interaction of proteins with the gut immune system, a process that has evolved to prevent systemic immune responses to ingested proteins. In addition, the oral administration of autoantigens has become clinically relevant and is being investigated as a treatment for human autoimmune diseases. (emphasis added).

One of the mechanisms of peripheral immune tolerance after orally administered antigens is the generation of regulatory T cells that mediate active suppression. (citations omitted).

It thus appears that regulatory T cells are normally generated during the course of immune responses, and they function by the production of suppressive cytokines.

Chen et al. provide further substantiation that antigen administration stimulates peripheral immune tolerance, or suppression, via the induction of regulatory T cells. More importantly, Chen et al. disclosed, as early as 1994, that oral administration of antigens is a biologically relevant method for inducing regulatory T cells and appreciated the interaction of proteins with the gut immune system, i.e. gastric mucosa.

Therefore, Applicants submit that a more accurate interpretation of the Wendling et al. disclosure is that mucosal routes of administration are apparently critical in treating autoimmune diseases with conserved heat shock proteins. Indeed, Wendling et al. recognized that it is the mucosa (which includes the nasal mucosa, but also includes the oral mucosa) that is responsible for the uptake of heat shock proteins, as stated in the fourth sentence of the second

full paragraph on page 2716: “for cross-reactive epitopes of bacterial hsps, it seems significant that they are taken up and presented in the gut mucosa where IL-10 (and TGF- $\beta$ ) biased T cells are generated due to the local cytokine environment.” (emphasis added). Further, in the second sentence of the fifth paragraph on page 2716, Wendling et al. state “The mucosal environment may well influence developing immune responses by promoting the generation of IL-10-producing T cells.” Thus, Wendling et al. actually support enablement of the present invention, in that they confirm that mucosal routes of administration of the claimed peptides has the *in vivo* effect Applicants have asserted all along.

Third and finally, with respect to the Examiner’s assertion that Anderton et al. teach that treating human diseases with the mycobacterial heat shock proteins of the present invention would be unpredictable, Applicants respectfully point out that the Anderton et al. reference is *not* focused on the mycobacterial heat shock proteins of the present invention but rather on the complexities of certain areas of altered peptide ligand (APL) technology. In view of this focus, Anderton et al. would not be expected to highlight APLs for which no complicating aspects were known. Indeed, the Anderton et al. reference does not portray heat shock proteins in any negative light, and the fact that the claimed heat shock proteins are not plagued by immunogenic unpredictability has already been documented of record.

Additionally, the Examiner asserts that Anderton et al. argue against the use of APLs in human autoimmune disorders, citing page 370, in the paragraph bridging columns one and two. However, the context of the cited paragraph is the comparison of the differing effects of *in vitro* and *in vivo* Th1 clone conversion to IL-4, IL-10 or TGF- $\beta$ , in a manner unrelated to the *in vivo* administration of heat shock proteins of the claimed invention, and thus the Examiner errs in attempting to extend the cited conclusion to the claimed heat shock proteins. More importantly, heat shock peptides according to the invention act by an entirely different mechanism, as corroborated by Wendling et al. (described above). Indeed, the only mention by Anderton et al. of heat shock proteins (“hsp”) is on page 368, second column, approximately in the middle of the page as follows:

APL of MBP (72-85) and the arthritis-related peptide 180-188 of mycobacterial heat shock protein 65 (hsp 65) were generated that showed increased binding affinities for the RT1B<sup>1</sup> rat class II molecule... [and] in co-immunization experiments it was found that the MBP APL specifically inhibited EAE but not arthritis, indicating direct effects on antigen-specific T cells.

Therefore, Anderton et al. refers both to MBP and to hsp APL, but then offers a conclusion only as to the MBP; the effects of the hsp 65 not disclosed at all.

Thus, the Examiner's broad conclusion regarding the inefficacy of APLs in human autoimmune disorders taken from page 370 does not refer to heat shock proteins at all. The reference to "antagonist or immune-deviating APL" on page 370 would not have been understood to refer to heat shock proteins because the paragraph on page 370 refers to a Th1 clone conversion mechanism that had already been shown the year before, by Wendling et al., would not apply to heat shock proteins, which instead induce IL-10-producing regulatory T cells. Therefore, the Examiner mischaracterizes the conclusions of Anderton et al., in which there are no negative representations or implications regarding heat shock proteins. Any controversy with respect to other non-heat shock protein APLs and any inability to achieve a different mechanism is therefore irrelevant to the claimed invention.

Additionally, Anderton et al. explain the differing effects of APLs on page 367 and in Figure 1: "APLs can be divided based on their ability to stimulate antigen-specific T cells." Thus, when APLs are used for TCR antagonism or immune deviation, both mechanisms work only toward existing , pathogenic Th1 cells, namely, antagonism to silence the Th1 cells and immune deviation to induce the switch from Th1 to Th2 cells. In contrast, regulatory T cells, often called Tr or Treg cells, form a separate group which are completely different from Th1 and Th2 cells. In fact, Tr cells are regulatory/inhibitory towards Th1 as well as Th2 cells. Therefore, it is clear that Anderton et al. do not disclose problems associated with APLs to induce regulatory T cells, but instead disclose the problems associated with the induction of Th2 cells by switching existing Th1 cells to Th2 cells. Thus, Applicants do not agree, and Anderton et al. do not represent, that *in vivo* animal studies are problematic in predicting human treatment, except as to transformation of pathogenic T cells, which Wendling et al. show, as described above, the claimed heat shock proteins of the present invention do not do. Of overriding

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importance is the fact that nothing within the Anderton et al. reference calls into question the assertions of Applicants with respect to the claimed heat shock peptides or their ability to function as described and claimed.

Parenthetically, the arthritis-related peptide 180-188 of mycobacterial heat shock protein 65 disclosed by the Anderton et al. reference is not within the scope of the pending claims in any case.

For all the foregoing reasons, pending claims 24-32 are in condition for allowance. Reconsideration of the rejections and allowance of pending claims 24-32 are respectfully requested.

Respectfully submitted,

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